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Noninferiority is (too) common in noninferiority trials

In their meta-analysis of 317 randomized trials that examined efficacy and safety of drugs, biologics, and medical devices in head-to-head comparisons, Flacco et al. [1] report that 97% (55 of 57) of industry-funded noninferiority/equivalence trials provided favorable results (defined as superiority or noninferiority of the experimental treatment) compared to 71% (20 of 28) of nonindustry-funded noninferiority/equivalence trials. We reviewed the data from our previously published meta-analysis of 175 noninferiority comparisons [2]. Overall, 83% (145 of 175) of the comparisons produced desirable favorable results (superiority or noninferiority for the experimental treatment). In contrast to Flacco et al. [1], there was no important difference in this percentage by type of funding source.

Figure 1 shows the combined risk ratios from random-effects meta-analyses by funding source, and the percentage of comparisons with favorable results. There was little evidence for heterogeneity in combined risk ratios (P Z 0.20 from chi-squared test) and percentages (P Z 0.49 from chi-squared test). The trials examined by Flacco et al. [1] were published in 2011, whereas our analysis was based on trials published between 1993 and 2009. It is therefore possible that the difference between industry-sponsored and other trials emerged in recent years. However, in our data set, we found no clear trend over time in this difference. Taken together, the data from these two meta-analyses show that a large majority of published noninferiority trials support the experimental treatment. The probability of getting a verdict of noninferiority in a noninferiority trial is greater than 80%. From the viewpoint of industry and other stakeholders, the noninferiority design is therefore a very ‘‘safe’’ design. The situation is more variable for superiority trials. The study by Flacco et al. [1] and another metaepidemiological study of trials from a range of medical specialties found that experimental treatments were superior in 68% to 74% of trials [3]. In contrast, two studies in oncology found that only 25% to 45% of trials produced results compatible with superiority of the experimental treatment [4,5].

There are valid reasons for choosing a noninferiority design when performing a trial. However, industry and other stakeholders may be tempted to choose the design for the wrong reasons; that is, to increase the chance of obtaining a favorable result even when a superiority design would have been more appropriate to answer the questions that really matter to patients. Therefore, the rationale for choosing the noninferiority design, the primary outcome, the noninferiority margin and the evidence for the supposed benefit of the experimental treatment should always be specified and consistently reported in study protocols, trial registries, and publications [6-8].

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Figure 1. Results of 175 comparisons from 170 noninferiority trials and percentage of comparisons favoring the experimental treatment (defined as superiority or noninferiority of the experimental treatment). Reanalysis of the data from Soonawala et al. [2].